Poster I-18

A Unified Nonlinear Signal Processing and System Identification Approach to Dynamic Pathway Identification From DNA Microarray Data

Najarian, Kayvan*[*1], Meyer, Ralph[2], Meyer, Martha[2]
[1]Computer Science Department, University of North Carolina at Charlotte, Charlotte, NC, USA; [2]Carolinas Medical Center, Charlotte, NC, USA

A hierarchical computational framework to predict and analyze the dynamic pathways from DNA Microarray data is proposed. This technique is designed to process microarray data captured at different times throughout the course of a study (e.g. a number of microarrays taken at different weeks during the healing process for a given disease treatment) and quantitatively discover and analyze the gene pathways involved in the process. At the first stage, using a recursive clustering techniques based on Independent Component Analysis (ICA), statically-independent clusters of genes are identified. This recursive process is automated and the optimal number of gene clusters is identified through an optimization process. In the second stage, a time-correlation matrix for the identified gene groups are formed which reveals the gene clusters predicted to form a pathway. During this process, the exact amount of time-lag among the genes in a pathway is predicted and visually represented. In the last stage, nonlinear Auto-Regressive eXogenous (ARX) model are trained to predict the mathematical relation among the genes involved in the pathway.

This hierarchical system has been applied to analysis of bone fracture healing process. Gene expression at the mRNA level for all known rat genes were measured by DNA microarrays for several weeks after fracture in young rats at 6 weeks of age, in adult rats at 26 weeks or age and in older rats at one year of age. The optimal clustering of these data was intended to help discover: 1) the normal progression of rapid fracture healing in young rats at the molecular level, and 2) why healing slows in the adult rats and stops in older rats prior to regaining normal skeletal strength. These findings suggest specific cytokines for administration to the fracture site to accelerate healing. Such treatment may decrease nonunion rates, reduce the time needed for fracture healing, and improve the quality of life for human patients. This study suggests that the number of genes involved in fracture healing is surprisingly large and involves many genes not presently thought of as being involved in skeletal repair. This study not only identities the role of these genes in normal progression of the healing process, but also describes the genetic roots of the delayed healing in adults. If the identified factors responsible for the impaired healing could be corrected through pharmacological intervention, it would greatly improve the well being of these patients. Some of the obtained results are shown in Figure 1: (a) the prototypes of three clusters (out of 105 clusters) and the expression patterns of the genes in their clusters, (b) the amount of correlation among each pair of clusters (red: highest correlation and blue lowest), and (c) the amount of time delay among the time delay among the time-correlated gene clusters.

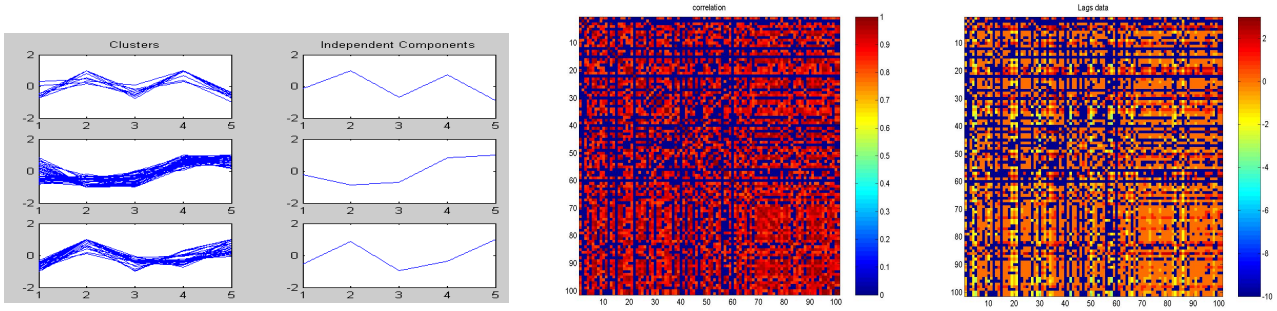

Figure 1. (a) Three independent components (prototypes) and the genes in their clusters (b) Correlation among gene clusters, (c) Time-lag among the gene clusters in a pathway.